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Chapter 55: Parkinson Disease

INTRODUCTION

- *Parkinson disease* (PD) has highly characteristic neuropathologic findings and a clinical presentation, including motor deficits and, in some cases, mental deterioration.

CLINICAL PRESENTATION

- PD develops insidiously and progresses slowly over many years.

GENERAL FEATURES

- Bradykinesia (slowness of movements) and at least one of the following: resting tremor, rigidity, or postural instability.

MOTOR SYMPTOMS

- Only two-thirds of PD patients have tremor at diagnosis, and some never develop it. Tremor, often with a pill-rolling motion, commonly affects the hands and may be asymmetric.
- Hypokinetic movements, decreased manual dexterity, difficulty standing from sitting, diminished arm swing, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (passing from a slow to a quickened pace), flexed posture, "freezing" at movement initiation, hypomimia (reduced facial animation), hypophonia (reduced voice volume), and micrographia.

AUTONOMIC AND SENSORY SYMPTOMS

- Bladder dysfunction, constipation, diaphoresis, fatigue, olfactory impairment, orthostatic intolerance, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea (drooling).

MENTAL STATUS CHANGES

- Anxiety, apathy, bradyphrenia (slowness of thought processes), cognitive impairment, depression, and hallucinosis/psychosis.

SLEEP DISTURBANCES

- Excessive daytime sleepiness, insomnia, obstructive sleep apnea, and rapid eye movement sleep behavior disorder.

DIAGNOSIS

- The clinical diagnosis of PD is outlined in **Table 55-1**.
- Laboratory or genetic testing cannot diagnose PD. Neuroimaging may be useful for excluding other diagnoses.
- Obtain a medication history to rule out medication-induced parkinsonism.

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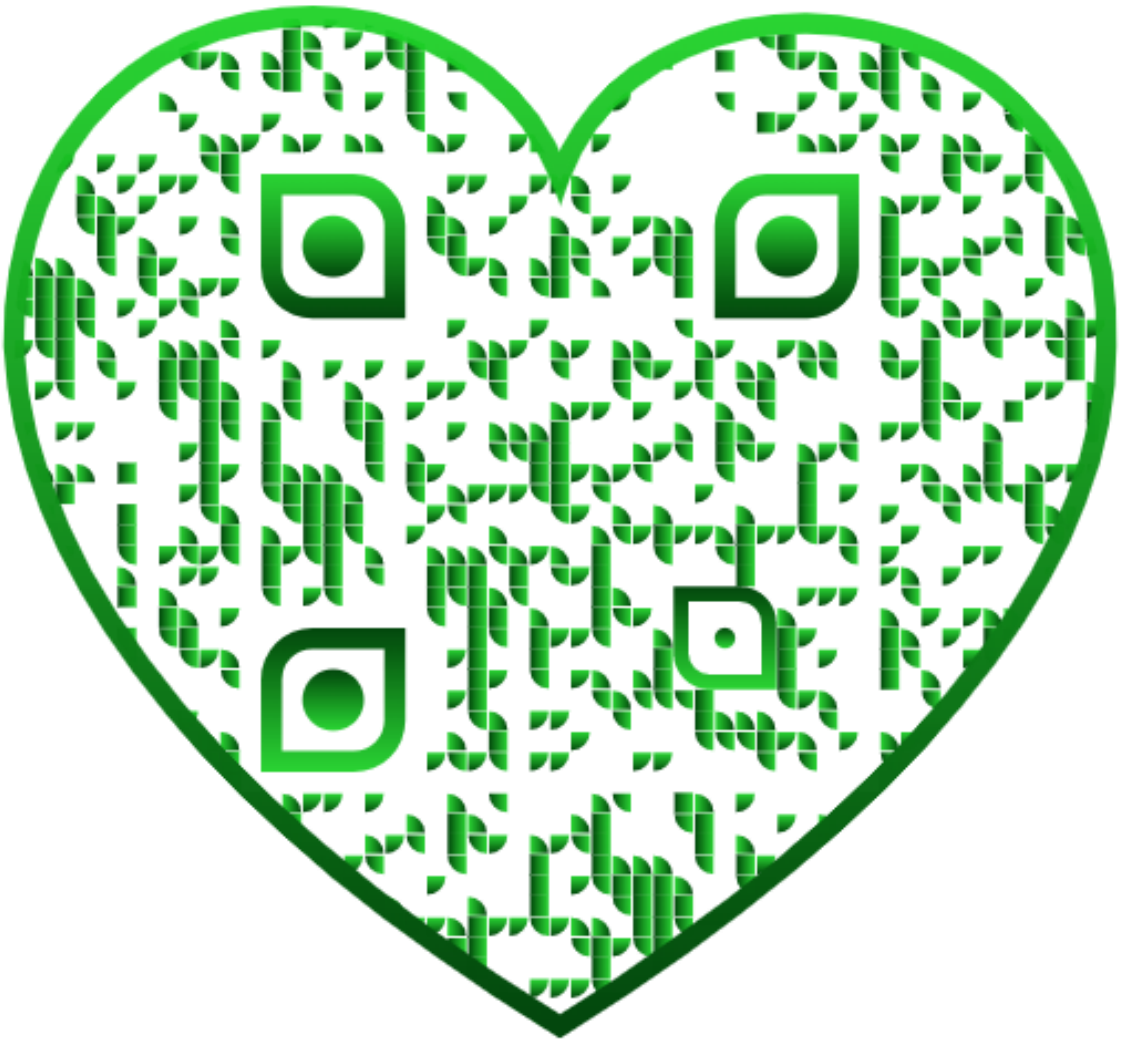

TABLE 55-1

Diagnostic Criteria and Differential Diagnosis for Parkinson Disease

Parkinson Disease

- Step 1: Presence of bradykinesia and at least one of the following: resting tremor, rigidity, or postural instability
- Step 2: Exclude other types of parkinsonism or tremor disorders
- Step 3: Presence of at least three supportive positive criteria:
  - Asymmetry of motor signs/symptoms
  - Unilateral onset
  - Progressive disorder
  - Resting tremor
  - Excellent response to carbidopa/levodopa
  - Levodopa response for 5 years or longer
  - Presence of levodopa dyskinesias

Differential Diagnosis

- Essential tremor
- Pharmacotoxicity (medication-induced)
  - Antiemetics (eg, metoclopramide, prochlorperazine)
  - Antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, olanzapine, risperidone, thioridazine)
  - Other medications (α-methyldopa, cinnarizine, flunarizine, tetrabenazine)
- Environmental toxicity (eg, manganese, organophosphates)
- Infections (eg, human immunodeficiency virus, subacute sclerosing panencephalitis)
- Metabolic disorder (eg, hypothyroidism, parathyroid abnormalities)
- Neoplasms, strokes, traumatic lesions involving the nigrostriatal pathways
- Normal-pressure hydrocephalus
- Parkinsonism with other neuronal system degenerations
  - Corticobasal ganglionic degeneration
- Multiple-system atrophies
- Progressive supranuclear palsy
- Familial (hereditary) parkinsonism
  - Autosomal dominant
    - α-Synuclein gene mutation (*PARK1* and *PARK4*)
    - L-responsive dystonia
    - Leucine-rich repeat kinase 2 (*LRRK2*) mutation
    - Rapid-onset dystonia-parkinsonism (DYT12)
    - Spinocerebellar ataxias (SCA2, SCA3)
  - Autosomal recessive
    - Wilson disease
    - Young-onset parkinsonism (DJ-1, parkin, PINK1)
  - X-linked recessive
    - Fragile X tremor/ataxia syndrome (FXTAS)
    - Lubag (DYT3 or Filipino dystonia-parkinsonism)

TREATMENT

- Goals of Treatment: To reduce symptoms, disability, and medication adverse effects while maintaining quality of life. Patient and caregiver

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education, exercise, and proper nutrition are essential.

- No treatments have been proven to slow or stop PD progression.

NONPHARMACOLOGIC THERAPY

- Exercise, physiotherapy, yoga, Tai Chi, dance, and Lee Silverman Voice Treatment-BIG Therapy can improve PD symptoms.
- Surgery, specifically deep brain stimulation, or focused ultrasound should be considered alongside medication for patients with frequent motor fluctuations or disabling dyskinesia or tremor.

PHARMACOLOGIC THERAPY

General Approach

- An algorithm for management of early to advanced PD is shown in **Fig. 55-1**. **Table 55-2** is a summary of available antiparkinsonian medications and their dosing, and **Table 55-3** shows adverse effect monitoring.
- For mild impairment, initial treatment often starts with a monoamine oxidase-B (MAO-B) inhibitor.
- All patients will eventually need **carbidopa/levodopa,** alone or with other agents.
- For motor fluctuations, increase carbidopa/levodopa frequency or add a catechol-*O*-methyltransferase (COMT) inhibitor, MAO-B inhibitor, adenosine receptor antagonist, or dopamine agonist.
- To manage carbidopa/levodopa–induced peak-dose dyskinesias, reduce the levodopa dose and/or add amantadine.

Figure 55-1

General approach to the management of early to advanced Parkinson disease. (*Age is not the sole determinant for medication choice. Other factors such as cognitive function and overall medication tolerability, especially in older patients, should be considered.)

TABLE 55-2

Dosing of Medications Used in Parkinson Disease[a]

Generic Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)
Adenosine-Receptor Antagonist		
Istradefylline	20	20–40
Anticholinergic Medications		
Benztropine	0.5–1	1–6
Trihexyphenidyl	1–2	6–15
Carbidopa/Levodopa Products		
Carbidopa/L-dopa	300[c]	300–2000[c]

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Carbidopa/L-dopa	300[c]	300–2000[c]
Carbidopa/L-dopa ODT	300[c]	300–2000[c]
Carbidopa/L-dopa CR	400[c]	400–2000[c]
Carbidopa/L-dopa IR/ER	435[c]	435–2450[c]
Carbidopa/L-dopa IR/ER	280[c]	
Carbidopa/L-dopa enteral suspension	1000[c]	1000–2000[c]
Carbidopa/L-dopa/entacapone	600[d]	600–1600[d]
Carbidopa	25	25–75
Foscarbidopa/foslevodopa subcutaneous injection	Varies	Varies
Levodopa	84	84–420
Dopamine Agonists		
Apomorphine	1–3	3–12
Apomorphine	16	16–96
Bromocriptine	2.5–5	15–40
Pramipexole	0.125	1.5–4.5
Pramipexole ER	0.375	1.5–4.5
Ropinirole	0.75	9–24
Ropinirole XL	2	8–24
Rotigotine	2	2–8
COMT Inhibitors		
Entacapone	200–600	200–1600
Opicapone	25–50	50
Tolcapone	300	300–600
MAO-B Inhibitors		
Rasagiline	0.5–1	0.5–1
Safinamide	50	50–100

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Selegiline	5–10	5–10
Selegiline ODT	1.25	1.25–2.5
Miscellaneous		
Amantadine	100	200–300
Amantadine ER	137	274
Amantadine ER	129	129–258

[a]Marketed in the United States for Parkinson disease.

[b]Dosages may vary.

[c]Dosages expressed as L-dopa component.

[d]Dosages expressed as entacapone component.

COMT, catechol-O-methyltransferase; CR, controlled-release; ER, extended-release; IR, immediate-release; MAO, monoamine oxidase; ODT, orally disintegrating tablet; XL, extended-release.

TABLE 55-3

Monitoring of Potential Adverse Effects of Pharmacotherapy for Parkinson Disease

Generic Name	Adverse Medication Effect	Monitoring Parameter	Comments
Amantadine	Confusion	Mental status; renal function	Reduce dosage; adjust dose for renal impairment
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon medication discontinuation
Benztropine and trihexyphenidyl	Anticholinergic effects, confusion, drowsiness	Dry mouth, mental status, bowel movements, urinary retention, vision	Reduce dose; avoid in elderly, and those with constipation, memory issues, or urinary retention history.
Carbidopa/L-dopa	Drowsiness	Mental status	Reduce dose
	Dyskinesias	Abnormal involuntary movements	Reduce dose; add amantadine
	Nausea	Nausea	Take with food (eg, nonprotein snack)
Istradefylline	Insomnia, dizziness, nausea, constipation	Sleep, nausea, bowel movements	Take in the morning; take with food
COMT Inhibitors			
Entacapone	Augmentation of L-dopa	See carbidopa/L-dopa; also	Reduce dose of L-dopa; antidiarrheal agents

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	adverse effects; also diarrhea	bowel movements	
Opicapone	Augmentation of L-dopa adverse effects, constipation	Mental status, abnormal involuntary movements, bowel movements	Reduce dose of L-dopa
Tolcapone	See entacapone; also liver toxicity	See carbidopa/L-dopa; also ALT/AST	See carbidopa/L-dopa; check ALT/AST at baseline and every dose increase, then every 2–4 weeks for 6 months; monitor afterward as needed.
Dopamine Agonists			
Apomorphine	Drowsiness	Mental status	Reduce dose
	Nausea	Nausea	Slow titration
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Bromocriptine	See pramipexole; also pulmonary fibrosis	Mental status; also chest radiograph	Reduce dose; chest radiograph at baseline and once yearly
Pramipexole and ropinirole	Confusion	Mental status	Reduce dose or discontinue
	Drowsiness	Mental status	Reduce dose; titrate dose slowly if initiating therapy
	Edema	Lower extremity swelling	Reduce dose or discontinue
	Hallucinations/delusions	Behavior, mental status	Reduce dose or discontinue
	Impulsivity	Behavior, mental status	Reduce dose or discontinue
	Nausea	Nausea	Titrate dose slowly; take with food
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Titrate dose slowly
Rotigotine	See pramipexole; also skin irritation at site of patch application	See pramipexole/ropinirole; also skin examination	See pramipexole/ropinirole; rotate patch application site
MAO-B Inhibitors			
Rasagiline	Nausea	Nausea	Take with food
Safinamide	Nausea	Nausea	Take with food
	Elevation in blood pressure	Blood pressure	Monitor blood pressure with a history of uncontrolled hypertension
	Insomnia	Sleep	Take in the morning

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Selegiline	Agitation/confusion	Mental status	Reduce dose
	Insomnia	Sleep	Administer dose earlier in day
	Hallucinations	Behavior, mental status	Reduce dose
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

Anticholinergic Medications

- **Anticholinergic** medication can improve tremor and dystonia but rarely bradykinesia or other disabilities. They are often used alongside other treatments.

  ✓ Adverse effects include dry mouth, blurred vision, constipation, and urinary retention. Serious reactions include forgetfulness, confusion, sedation, depression, and anxiety. (see **Table 55-3**). Older patients and those with cognitive deficits are at higher risk for central anticholinergic effects.

Amantadine

- **Amantadine** provides modest benefit for tremor, rigidity, and bradykinesia and is used for levodopa-induced dyskinesia.
- There are multiple formulations available for use (see Table 55-2).
- Doses should be reduced in renal dysfunction (100 mg/day with creatinine clearances of 30–50 mL/min [0.50–0.84 mL/sec], 100 mg every other day for creatinine clearances of 15–29 mL/min [0.25–0.49 mL/sec], and 200 mg every 7 days for creatinine clearances less than 15 mL/min [0.25 mL/sec]) and those on hemodialysis.

  ✓ Common adverse effects (see **Table 55-3**) include livedo reticularis (a diffuse mottling of the skin in the upper or lower extremities), which is reversible.

Levodopa and Carbidopa/Levodopa

- **Levodopa** is the precursor to dopamine, and when combined with a peripheral L-amino acid decarboxylase (L-AAD) inhibitor (**carbidopa** or **benserazide**), it remains the most effective treatment for PD symptoms.
- Levodopa is converted to dopamine by L-AAD in the central nervous system (CNS) and periphery. Carbidopa can block peripheral L-AAD, enhancing CNS penetration and reducing dopamine side effects like nausea and hypotension. Benserazide, another L-AAD inhibitor, is not available in the United States.
- The usual maximal levodopa dose tolerated is approximately 1000 to 1500 mg/day.
- About 75 mg of carbidopa is needed to block peripheral L-AAD, though some may need more. Controlled-release carbidopa/levodopa is available (**Table 55-2**). For those with swallowing difficulties, an orally disintegrating tablet and a sprinkle capsule (Rytary) are options.
- After oral levodopa, peak plasma time varies between individuals. Meals delay but antacids promote gastric emptying. Absorption occurs in the proximal duodenum via a saturable transport system, so high-protein meals can reduce bioavailability.
- Levodopa is not bound to plasma proteins, with a half-life of about 1 hour. Carbidopa or benserazide extends it to 1.5 hours, and adding a COMT inhibitor like **entacapone** extends it to 2–2.5 hours.

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- Sinemet CR and Rytary are 70% and 75% bioavailable compared to the standard immediate-release carbidopa/levodopa formulation.

  ✓ Levodopa-related motor complications can be disabling but manageable (**Table 55-4**). The risk is about 10% per year and may occur 5–6 months after starting treatment. Higher doses and younger age at PD onset are risk factors.

TABLE 55-4

Common Motor Complications and Possible Initial Treatments

Complication and Management
End-of-dose "wearing off": Related to reduced neuronal dopamine storage and levodopa's short half-life.
Increase carbidopa/levodopa frequency; consider adding a COMT inhibitor, MAO-B inhibitor, istradefylline, amantadine, or dopamine agonist; switch to extended-release carbidopa/levodopa (Rytary); or use L-dopa inhalation or subcutaneous apomorphine
"Delayed on" or "no on" response: Can result from delayed gastric emptying or reduced duodenal absorption.
Give carbidopa/levodopa on empty stomach; use carbidopa/levodopa ODT or crush or chew regular tablets and take on an empty stomach; avoid carbidopa/levodopa CR; use apomorphine subcutaneous or sublingual or levodopa inhalation.
Start hesitation ("freezing"): An episodic inhibition of lower limb movement, worsened by anxiety, may increase falls.
Increase carbidopa/levodopa dose; add a dopamine agonist or MAO-B inhibitor; use physical therapy with assistive devices or sensory cues (eg, rhythmic commands, stepping over objects).
Peak-dose dyskinesia: Involuntary choreiform movements of the neck, trunk, and extremities often occur at peak dopamine levels.
Provide smaller doses of carbidopa/levodopa at the same or increased dosing frequency; reduce dose of adjunctive dopamine agonist; add amantadine

COMT, catechol-*O*-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

Adenosine Receptor Antagonist

- **Istradefylline** is used adjunctively to levodopa for "off" episodes (see **Table 55-2**). For patients who smoke >20 cigarettes, a day use the 40-mg dose.

  ✓ Common adverse effects include insomnia, hallucination, nausea, and constipation.

  ✓ Metabolized by CYP1A1 and CYP3A4, it has an 80-hour half-life. Avoid strong CYP3A4 inducers and reduce dose with strong inhibitors.

Monoamine Oxidase-B Inhibitors

- Selective MAO-B inhibitors (**rasagiline**, **safinamide**, **selegiline**) are available for PD (see **Table 55-2**).
- Rasagiline and selegiline irreversibly inhibit MAO-B due to their propargylamine moiety, unlike the reversible safinamide. At therapeutic doses, all three primarily inhibit MAO-B over MAO-A.
- Using MAO-B inhibitors with meperidine or certain opioids is contraindicated due to serotonin syndrome, but they can be used with serotonergic antidepressants if needed.
- As monotherapy in early PD, selegiline and rasagiline modestly improve motor function.

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- All can provide up to 1 extra hour of "on" time when used adjunctively.
- Selegiline boosts levodopa peak effects, potentially worsening dyskinesias or delusions. Its metabolites are L-methamphetamine and L-amphetamine. The oral disintegrating tablet may improve response and reduce adverse effects.

  ✓ Selegiline may cause agitation, insomnia, hallucinations, and orthostatic hypotension. Rasagiline and safinamide are generally well tolerated with few gastrointestinal or psychiatric effects.

Catechol-*O*-Methyltransferase Inhibitors

- **Tolcapone, entacapone,** and **opicapone** are used with carbidopa/levodopa to prevent its peripheral conversion, increasing levodopa's area under the curve (AUC) by ~35%, adding ~1–2 hours of "on" time (longer with opicapone), and reducing levodopa dosage requirements. Avoid nonselective MAO inhibitors to prevent inhibition of normal catecholamine metabolism pathways.
- **Table 55-2** outlines dosing. Opicapone is dosed once daily, while entacapone is taken with each carbidopa/levodopa dose, up to eight times daily.

  ✓ Tolcapone's use is limited by the risk of fatal liver toxicity, necessitating strict monitoring. Entacapone does not cause hepatotoxicity.

  ✓ Dopaminergic adverse effects may occur and are managed by reducing the carbidopa/levodopa dose. Brownish-orange urine may occur.

Dopamine Agonists

- The ergot derivative **bromocriptine** and the nonergots **pramipexole, rotigotine,** and **ropinirole** help reduce "off" periods and spare levodopa in patients with fluctuating levodopa response when used adjunctively.
- Titrate the dose slowly to enhance tolerability, and find the optimal dose (see **Table 55-2**).
- Nonergots are effective as monotherapy in mild-to-moderate PD and as adjuncts to levodopa in patients with motor fluctuations, offering a safer option.
- **Pramipexole** is primarily renally excreted, and the dose must be adjusted in renal insufficiency.
- **Ropinirole** is metabolized by cytochrome P4501A2; fluoroquinolones and cigarette smoking may alter clearance.
- **Rotigotine** patch provides continuous release over 24 hours, and disposition is not affected by hepatic or renal impairment.
- **Apomorphine**, a nonergot dopamine agonist, is given as a subcutaneous "rescue" injection for advanced PD patients with intermittent "off" episodes. It triggers an "on" response in 20 minutes, lasting up to 100 minutes. Due to nausea, vomiting, and orthostatic hypotension risks, apomorphine initiation requires healthcare monitoring. Doses are individualized based on tolerability and orthostatic blood pressure.

  ✓ Common adverse effects (**Table 55-3**) include vivid dreams and sleep attacks. Adding levodopa may worsen dyskinesias. Manage hallucinations or delusions by reducing or stopping the drug and, if needed, adding **clozapine, quetiapine**, or **pimavanserin.**

  ✓ **Bromocriptine** is not commonly used given its safety profile, which includes a risk of pulmonary fibrosis.

  ✓ Dopamine agonists pose less motor complication risk than levodopa, making them preferable for younger patients. Carbidopa/levodopa may suit older patients better due to psychosis and orthostatic hypotension risks from dopamine agonists. Avoid dopamine agonists in patients with cognitive issues or dementia.

EVALUATION OF THERAPEUTIC OUTCOMES

- Comprehensive monitoring is essential (**Table 55-5**). Educate patients and caregivers to record medication doses, administration times, and "on" and "off" periods.
- Stop any medications that may worsen motor symptoms, memory, falls, or behavior if possible.

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TABLE 55-5

Monitoring and Education for Parkinson Disease Therapy

1. Monitor medication times. Educate patients that immediate-release carbidopa/levodopa is best absorbed on an empty stomach but is often taken with food (nonprotein snacks) to reduce nausea. Avoid taking selegiline late to prevent insomnia.
2. Ensure patients and caregivers understand the medication regimen, eg, COMT inhibitors enhance L-dopa effects and should not be stopped without consulting a clinician.
3. Monitor dose-by-dose medication effects, including response, dyskinesias, "wearing-off," dizziness, nausea, orthostasis, or hallucinations (**Tables 55-3** and **55-4**). Suggest ways to alleviate these or encourage discussing these with the clinician.
4. Monitor caregiver involvement in detecting abnormal behaviors, dyskinesias, falls, hallucinations, impulsivity, memory issues, mood changes, and sleep disorders.
5. Monitor for nonadherence and inquire about reasons (eg, dosing convenience, cost, adverse effects), then offer solutions.
6. Monitor for medications that can worsen Parkinson's motor symptoms, like D2-receptor blockers.
7. Monitor for medications worsening nonmotor symptoms, and assess if an anticholinergic is causing confusion or cognitive impairment.

See Chapter 82, Parkinson Disease, authored by Jessa M. Koch and Khashayar Dashtipour, for a more detailed discussion of this topic.

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